

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



B1

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6: A61K 31/19, 31/20, 31/22, 31/35		A3	(11) International Publication Number: WO 95/10271 (43) International Publication Date: 20 April 1995 (20.04.95)
(21) International Application Number: PCT/US94/11492 (22) International Filing Date: 12 October 1994 (12.10.94)		(74) Agents: NEEDLE, William, H. et al.; Needle & Rosenberg, P.C., 127 Peachtree Street NE, Suite 1200, Atlanta, GA 30303-1811 (US).	
(30) Priority Data: 08/135,661 12 October 1993 (12.10.93) US 08/207,521 7 March 1994 (07.03.94) US		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ).	
(60) Parent Application or Grant (63) Related by Continuation US Filed on 08/207,521 (CIP) 7 March 1994 (07.03.94)		Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(71) Applicant (for all designated States except US): THE GOVERNMENT OF THE UNITED STATES OF AMERICA, represented by THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES [US/US]; National Institutes of Health, Office of Technology Transfer, Box OTT, Bethesda, MD 20892-9902 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): SAMID, Dvorit [US/US]; 13 Tapiola Court, Rockville, MD 20850 (US).		(88) Date of publication of the international search report: 22 June 1995 (22.06.95)	
(54) Title: PHENYLACETIC ACID DERIVATIVES ALONE OR IN COMBINATION WITH OTHER COMPOUNDS AGAINST NEOPLASTIC CONDITIONS AND OTHER DISORDERS			
(57) Abstract <p>Compositions and methods of treating various disorders by administering a therapeutically effective amount of phenylacetate or pharmaceutically acceptable derivatives thereof or derivatives thereof alone or in combination or in conjunction with other therapeutic agents including retinoids, hydroxyurea, and flavonoids. Intravesicle methods of treatment of cancers phenylacetate. Pharmacologically-acceptable salts alone or in combinations and methods of preventing AIDS and malignant conditions, and inducing cell differentiation are also aspects of this invention. A product as a combined preparation of phenylacetate and a retinoid, hydroxyurea, or flavonid (or other mevalonate pathway inhibitor) for simultaneous, separate, or sequential use in treating a neoplastic condition in a subject. Methods of modulating lipid metabolism and/or reducing serum triglycerides in a subject using phenylacetate.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 94/11492

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K31/19 A61K31/20 A61K31/22 A61K31/35

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EXPERIENTIA, vol.27, 1971 pages 860 - 861 W. NEISH 'Phenylacetic acid as a potential therapeutic Agent for the treatment of human cancer.' cited in the application see the whole document ---	1-6, 60-64,69
Y	DRUGS EXP. CLIN. RES., vol.12, 1986 pages 11 - 16 S.R. BURZYNSKI 'Preclinical studies on Antineoplaston AS2-1 and Antineoplaston AS2-5' see the whole document ---	1-6, 60-64,69 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

2

Date of the actual completion of the international search

Date of mailing of the international search report

27 January 1995

26.05.95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Stierman, B

NATIONAL SEARCH REPORT

International Application No
PCT/US 94/11492

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MOL. CELL. ENDOCRINOL., vol.80, no.1-3, 1991 pages 183 - 192 Y. SHECHTER ET AL. 'Hydroxyphenyl acetate derivatives inhibit protein tyrosine kinase activity and proliferation in Nb2 rat lymphoma cells and insulin-induced lipogenesis in rat adipocytes' see the whole document ---	1-6, 60-64,69
P,Y	CANCER RES., vol.52, no.7, 1992 pages 1988 - 1992 D. SAMID ET AL. 'Phenylacetate: A novel nontoxic inducer of tumor cell differentiation' see the whole document ---	1-6, 60-64, 69,95-98
Y	EP,A,0 069 232 (S. BURZYNSKI) 12 January 1983 see claim 3 ---	1-6, 60-64,69
Y	BR. J. HEMATOL., vol.79, 10 October 1991 pages 81 - 83 D. SAMID ET AL. 'Interferon in combination with antitumourigenic phenyl derivatives: potentiation of IFN alpha activity in-vitro' see the whole document ---	1-6, 60-64,69
Y	CANCER LETT (NETHERLANDS), NOV 19 1990, VOL. 55, NO. 1, PAGE(S) 1-5, ABEMAYOR E ET AL 'Effects of retinoic acid on the in vivo growth of human neuroblastoma cells.' see the whole document ---	1-6, 60-64,69
P,Y	CANCER LETT (NETHERLANDS), JUN 15 1993, VOL. 70, NO. 1-2, PAGE(S) 15-24, CINATL J ET AL 'In vitro differentiation of human neuroblastoma cells induced by sodium phenylacetate.' see the whole document ---	1-6, 60-64,69
P,X	IN VITRO CELL DEV BIOL (UNITED STATES), MAR 1993, VOL. 29A (3 PT 1, PAGE(S) 189-91, GORSKI GK ET AL 'Synergistic inhibition of human rhabdomyosarcoma cells by sodium phenylacetate and Tretinoin [letter]' see the whole document ---	1-6, 60-64,69
2		-/-

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 94/11492

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT*

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	PROCEEDINGS OF THE AMERICAN ASSOC. FOR CANCER RESEARCH ANNUAL MEETING, vol.35, March 1994 page 419 WADA R ET AL 'Effects of phenylacetate and its interaction with retinoic acid on human neuroblastoma differentiation' see abstract ---	1-6, 60-64,69
P,X	J INVEST DERMATOL (UNITED STATES), SEP 1994, VOL. 103, NO. 3, PAGE(S) 335-40, LIU L ET AL 'Differentiation of cultured human melanoma cells induced by the aromatic fatty acids phenylacetate and phenylbutyrate.' see the whole document ---	1-6, 60-64, 69,95-98
Y		95-98
P,X	J. UROL., vol.151, no.5, May 1994 page 491A WOOD C G ET AL 'Phenylacetate and retinoic acid act synergistically to promote cellular differentiation in the prostate cancer cell lines LNCaP' see abstract -----	1-6, 60-64,69

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 94/ 11492

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Please see attached sheets!
2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please see attached sheets!
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

For further information please see attached sheets ...!

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-6, 48-52, 60-64, 69, 89, 95-98

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

LACK OF UNITY OF INVENTION

1. Use of a phenylacetic acid derivative falling under the formula in claim 1 in combination with a retinoid for the manufacture of a medicament for the treatment of a neoplastic condition, use of said phenylacetic acid derivatives applied intravesically for the treatment of neoplastic condition, compositions containing said phenylacetic acid derivative and a retinoid; monitoring the bioavailability of the phenylacetic acid derivative in neoplastic condition; use of said phenylacetic acid derivative in the treatment of neoplastic condition in a subject resistant to radiation and chemotherapy.
(Claims 1-6,48-52,60-64,69,89,95-98)
2. Use of a phenylacetic acid derivative falling under the formula in claim 1 in combination with an inhibitor of the mevalonate pathway for the manufacture of a medicament for the treatment of a neoplastic condition, compositions containing said phenylacetic acid derivative and a vastatin.
(Claims 7-18,20,21-31,56-59,68)
3. Use of a phenylacetic acid derivative falling under the formula in claim 1 in combination with an inhibitor of the mevalonate pathway for the manufacture of a medicament for the treatment of papillomavirus infection.
(Claim 19 as far as not comprised in subject 2)
4. Use of a phenylacetic acid derivative falling under the formula in claim 1 in combination with a flavonoid for the manufacture of a medicament for the treatment of a neoplastic condition.
(Claims 32-37)
5. Use of a phenylacetic acid derivative falling under the formula in claim 1 in combination with hydroxyurea for the manufacture of a medicament for the treatment of a neoplastic condition, compositions containing said phenylacetic acid derivative and hydroxyurea.
(Claims 38-41,65-67,70)
6. Use of a phenylacetic acid derivative falling under the formula in claim 1 for the manufacture of a medicament for modulating lipid metabolism.
(Claims 42-47)
7. Use of a phenylacetic acid derivative falling under the formula in claim 1 for the manufacture of a medicament for sensitizing a subject to radiation therapy.
(Claims 53-55)
8. Use of a phenylacetic acid derivative falling under the formula in claim 1 for the manufacture of a medicament for inhibiting the production of IL-6 in a cell.
(Claims 71-74)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

9. Use of a phenylacetic acid derivative falling under the formula in claim 1 for the manufacture of a medicament for inducing the production of TGF alpha in a cell.
(Claims 75-78,92-94)
10. Use of a phenylacetic acid derivative falling under the formula in claim 1 for the manufacture of a medicament for inhibiting the production of TGF-beta2 in a cell.
(Claims 79-81)
11. Use of a phenylacetic acid derivative falling under the formula in claim 1 for the manufacture of a medicament for the treatment of AIDS-associated dysfunction of the central nervous system.
(Claims 82-84)
12. Use of a phenylacetic acid derivative falling under the formula in claim 1 for the manufacture of a medicament for enhancing immunosurveillance.
(Claims 85-87)
13. Monitoring the bioavailability of a phenylacetic acid derivative of formula 1 as far as not comprised in subject 1.
(Claims 88,90,91)

The problem to be solved by the present application is to provide a treatment for a number of different diseases and health problems, e.g. neoplastic conditions, viral infection, etc.

The solution proposed in the present application is to use a phenylacetic acid derivative according to the formula in claim 1 alone or in combination with other compounds as an active therapeutic substance.

The common technical feature and therefore the linking inventive concept is the use of a phenylacetic acid derivative of the formula drafted in claim 1 as the therapeutic substance.

In EXPERIENTIA, Vol. 27, 1971, pp. 860-861, the use of phenylacetic acid and its derivatives (including sodium phenylacetate) for the treatment of human cancer is disclosed.

In DRUGS EXP. CLIN. RES., Vol. 12, 1986, pp.11-16, the use of Antineoplaston AS2-1, containing phenylacetic acid, against breast cancer is described.

It is apparent from these documents that the use of phenylacetic acid derivatives as active therapeutic substances is not novel. In the absence of a special technical feature linking the different specified therapeutic applications, the application lacks unity of invention and must be divided a posteriori according to the different uses claimed.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

Concerning the combinations of a phenylacetic acid derivative together with another compound for the treatment of a neoplastic condition, the following has to be remarked:

From the above cited documents the use of phenylacetic acid derivatives for the treatment of neoplastic disease is known. Therefore the phenylacetic acid derivatives cannot be the common inventive concept linking all the different combinations and their use in the treatment of neoplastic disease.

The man skilled in the art knows that the different groups of compounds which the applicant combines with the phenylacetic acid derivative differ substantially from each other in their structure and mode of action. Therefore there is no novel inventive concept linking those different groups of combinations and so they form each a separate subject.

In the present application no further technical feature(s) can be distinguished that can be regarded as a "special technical feature" involved in the technical relationship among the different inventions. Consequently, the present application lacks unity of invention, and the different solutions not belonging to a common inventive concept are identified as different subjects listed in the communication pursuant to Article 17(3)(a) PCT. Each of the inventions listed is a distinct invention, characterised by its own special technical feature, defining the contribution which each of the claimed inventions, considered as a whole, makes over the prior art, i.e. the specific features of the individual therapeutic applications.

Searching these different subjects would have caused major additional searching efforts.

Only the first subject was searched.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

MEANINGFUL SEARCH NOT POSSIBLE OR INCOMPLETE SEARCH

Remark: Although claims 1-55, 71-87, 92-98 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
See also ANNEX I and II.

In view of the large number of compounds which are theoretically defined by the Markush formula of claim 1 the search had to be restricted for economic reasons. Expressions like "retinoid", "vastatin", "flavonoid" etc. do not make sufficiently clear which compounds are meant. A compound is not sufficiently defined by its activity (e.g. inhibitor of the mevalonate pathway). The search had therefore to be restricted to the compounds explicitly mentioned in the claims and to the general inventive concept.

Incomplete search

Claims searchable completely: 43, 44, 46, 47, 51, 52, 54, 55, 66, 67, 73, 74,
77, 78, 80, 81, 83, 84, 86, 87, 90-94, 96, 97;

Claims searchable incompletely: 1-42, 45, 48-50, 53, 56-65, 68-72, 75, 76, 79,
.82, 85, 88, 89, 95, 98.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 94/11492

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0069232	12-01-83	US-A-	4470970	11-09-84
		AU-B-	551109	17-04-86
		AU-A-	8423982	06-01-83
		CA-A,C	1188218	04-06-85
		JP-B-	7029925	05-04-95
		JP-A-	58010521	21-01-83
		JP-A-	5058886	09-03-93
		JP-A-	5032548	09-02-93
		US-A-	4558057	10-12-85
		US-A-	4559325	17-12-85